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Microbiological and epidemiological aspects of Rotavirus and enteric Adenovirus infections in hospitalized children in Italy

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SUMMARY

Rotaviruses and enteric adenoviruses are the most important causative agents of acute infantile gastroenteritis worldwide. From July 2005 to June 2007, 445 stool specimens from pediatric patients hospitalized with acute diarrhea were collected and tested for the presence of rotaviruses and enteric adenoviruses using an immunochromatographic assay. Rotavirus infection was detected in 123 cases (27.6%, ranging from 31.7% in 2005-2006 to 24.2% in 2006-2007); adenovirus infection occurred in 17 cases (3.8%, 13 cases in 2005-2006 (6.3%) and 4 cases in 2006-2007 (1.7%). The highest prevalence was seen in children from 13 to 24 months for rotaviruses, and in children from 25 to 36 months for adenoviruses. Rotavirus infection was detected with significantly higher frequency in children up to 36 months old (32.0%) compared to the older children (19.9%) ($P<0.01$). Mixed infections were observed in 10 cases (6 rotavirus-adenovirus, and 4 rotavirus-*Salmonella* spp.). Rotavirus infection was found predominantly in winter and spring with respect to autumn ($P<0.001$) or summer ($P<0.05$), with a peak in February. Adenovirus infection had a major epidemic period in spring 2006, peaking in March. Finally, this study indicates that many patients acquired rotavirus infection (37.4%), and enteric adenovirus infection (41.2%) during hospitalization for other underlying diseases.

KEY WORDS: Rotavirus, Adenovirus type 40/41, Acute gastroenteritis, Epidemiology, Children, Nosocomial infections, Italy

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INTRODUCTION

Acute gastroenteritis is one of the most common illnesses in humans. Viruses are recognized as important causes of this disease, particularly in children (Bon *et al.*, 1999; Wilhelmi *et al.*, 2003; Caracciolo *et al.*, 2007; Phan *et al.*, 2007). Group A rotaviruses (HRV) are the major cause of pediatric acute gastroenteritis worldwide followed, to a lesser extent, by enteric adenoviruses types 40 and 41 and other viral agents (Logan *et al.*, 2006). Globally, an estimated 702,000 children die each year from rotavirus diarrhea (Cunliffe *et al.*, 2005), the vast majority of whom are in developing countries (Wilhelmi *et al.*, 2003). Children under 5 years of age are particularly prone, and infection is predominant among those aged 6-24 months. Rotaviruses are classified into serogroups A through G, but Group A rotaviruses have the greatest epidemiological importance (Wilhelmi *et al.*, 2003).

Rotaviruses are also a frequent cause of nosocomial infection in children who are hospitalized for other reasons (Gleizes *et al.*, 2006). The high mortality rates caused by rotaviruses have accelerated the development of rotavirus vaccines. Recently, two new vaccines have been developed and have proven to be safe and efficacious.

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(Vesikari *et al.*, 2006; Ruiz-Palacios *et al.*, 2006). Enteric adenoviruses, including serotypes 40 and 41, are one of the commonest causes of pediatric viral gastroenteritis, secondary only to rotaviruses (Grimwood *et al.*, 1995). The incidence of enteric adenovirus infection is variable. In industrialized countries, the incidence varies from 1% to 8%, whereas in developing countries it varies from 2% to 31% (Wilhelmi *et al.*, 2003).
In Italy, there is limited epidemiological data about viral gastroenteritis in hospitalized children and a nationwide surveillance system for rotavirus or enteric adenovirus infection is lacking. The present 2-year study, carried out in the "Santa Maria Goretti" Hospital in Latina, Italy, examined the annual occurrence, relative frequencies and seasonal distribution of rotavirus and enteric adenovirus infection in hospitalized children with acute gastroenteritis. The role of coinfections with other diarrheagenic pathogens and the presence of nosocomial infections were investigated.

MATERIALS AND METHODS

Study area and collection of fecal specimens

The study area was the city of Latina, a medium-sized city of about 120,000 inhabitants with a surrounding area of ~150,000, located in central Italy. Fecal samples (one per child) were obtained from 445 children aged 0 to 13 years admitted to the Pediatric ward of the "Santa Maria Goretti" Hospital in Latina from July 2005 to June 2007. The median age of patients was 37 months. The age distribution in the periods 2005-2006 and 2006-2007 was similar. All consecutive infants with acute diarrhea were divided into seven age groups: 0-6 months, 7-12 months, 13-24 months, 25-36 months, 37-48 months, 49-60 months, more than 60 months, and were included in the study. Diarrhea was defined as the occurrence of three or more unformed (loose or watery) stools within a 24-hour period.

Rotavirus and Adenovirus detection

Stool samples were analyzed for Group A human Rotavirus and Enteric Adenovirus types 40/41 using an immunochromatographic technique (ICT) (VIKIA Rota-Adeno, bioMérieux, Marcy l'Etoile, France) according to the instructions of the manufacturer. This test is a qualitative method based on the association of monoclonal antibodies specific to rotaviruses and enteric adenoviruses respectively, and uses immunological reactions performed on a test strip by migration.

Examination of other enteropathogens

Rotavirus-positive or adenovirus-positive stool specimens were examined for *Salmonella* spp. and *Shigella* spp. Fecal samples were inoculated into selenite broth. After incubation at 35°C for 12-18 hours, selenite broth was inoculated in Hektoen agar at 35°C for 18-24 hours. Suspected colonies were identified using standard biochemical and serological techniques. Testing of other potentially pathogenic enteric microorganisms was performing depending on the physician's request.

Nosocomial infections

Hospital infections with rotaviruses or adenoviruses were diagnosed when the symptoms of acute diarrhea were observed in children hospitalized for other reasons at least 72 h after admission and up to 24 h after discharge. Moreover, we studied the correlation of rotavirus and adenovirus nosocomial infections with age, sex and seasons.

Statistical analysis

The statistical significance of the data was examined by a chi-square test (χ^2) and a probability value (P) of <0.05 was regarded as statistically significant.

RESULTS

Study of prevalence

Out of 445 stool specimens tested by the ICT method, 123 (27.6%) were positive for rotaviruses: 65 cases in 2005-2006 (31.7%) and 58 cases in 2006-2007 (24.2%). Moreover, adenovirus infections accounted for 3.8% (17 cases): 6.3% in 2005-2006 (13 cases), 1.7% in 2006-2007 (4 cases). Mixed infections were observed in 10 cases (Table 1).

Age and gender distribution

Out of 123 HRV positive patients, 74% (91 patients) were under 36 months of age; 14.6% (18 patients) were 37 to 60 months, and 11.4% (14 patients) were older than 60 months. The preva-

TABLE 1 - *Prevalence of rotavirus infections, adenovirus infections, and coinfections, in hospitalized children with acute gastroenteritis, July 2005 to June 2007, Latina, Italy.*

Period	*Samples No.*	*Rotavirus positive No. (%)*	*Adenovirus positive No. (%)*	*Rotavirus + Adenovirus No. (%)*	*Rotavirus + Salmonella spp. No. (%)*
2005-2006	205	65 (31.7)	13 (6.3)	4 (1.9)	2 (0.9)
2006-2007	240	58 (24.2)	4 (1.7)	2 (0.8)	2 (0.8)
2005-2007	445	123 (27.6)	17 (3.8)	6 (1.3)	4 (0.9)

lence of detection of rotaviruses in children less than 36 months of age (32.0%) was significantly different from that for the older children (19.9%) (P<0.01).

Rotavirus infection was most prevalent in children in the group ages 13 to 24 month (41.2%) and was the second most prevalent in children from 25 to 36 months of age (37.3%), although infections were also seen in all age groups (Figure 1). There was no difference in age distribution between the period 2005-2006 and 2006-2007.

Adenovirus infection was most prevalent in the group age 25 to 36 months (6.8%), but was detected in all age groups (Figure 1).

Rotavirus detection rates between genders showed 68 rotavirus positive out of 233 samples of male infants (29.2%) and 55 out of 212 samples of female infants (25.9%). This difference was statistically insignificant (P>0.05). Also, adenovirus infections were more frequent among boys than girls, but this difference was statistically insignificant (P>0.05).

Seasonality

The seasonality of rotavirus and adenovirus infection was also determined and is shown in Figure 2 and Figure 3, respectively. In the two years of the study, rotaviral diarrhea was significantly more frequent in winter and spring than in autumn (P<0.001) or summer (P<0.05). The prevalence trend was: winter (48 cases, 39.0%), spring (47 cases, 38.2%), summer (26 cases, 21.2%), autumn (2 cases. 1.6%). The incidence peaked in February with 18 cases in 2006 (27.7% of cases) and 12 cases in 2007 (20.7%) (Figure 2). 75.6% of the rotaviral infections were diagnosed

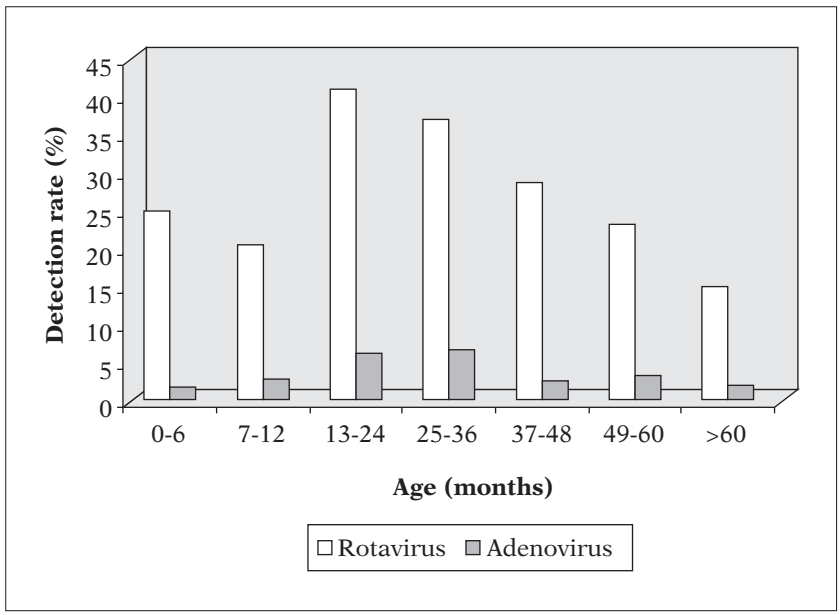

FIGURE 1 - *Distribution of rotavirus and enteric adenovirus infections by age, July 2005 to June 2007.*

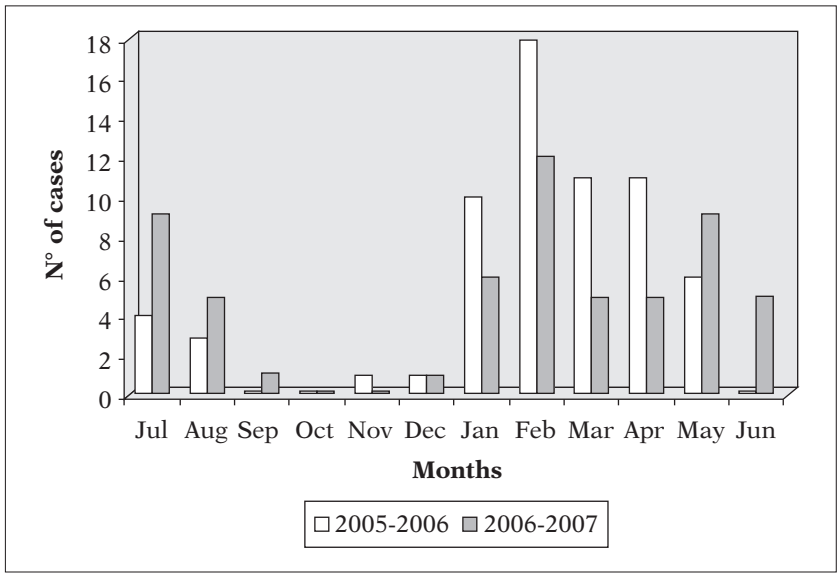

FIGURE 2 - *Monthly distribution of rotavirus infections in children with acute gastroenteritis, July 2005 to June 2007.*

between January and May. The distribution of cases of rotavirus infection during the two years of the survey was very different. In fact, in 2005-2006 HRV infection presented a seasonal pattern with a major prevalence in winter (44.6%) and spring (43.1%) than in summer (10.8%, $P<0.01$) or autumn (1.5%, $P<0.001$). In 2006-2007, except autumn where there was only one case, cases were spread in a uniform manner throughout the seasons (Figure 2).

Adenovirus infection, which occurred in relatively small numbers, had a major epidemic period in spring 2006, peaking in March (4 cases, 30.8%), and February and April 2007 (Figure 3).

Coinfections

Ten cases had mixed infections with pathogens associated with diarrhea. In 2005-2006, two patients were infected with both *Salmonella* spp. and rotaviruses, and four patients with ro-

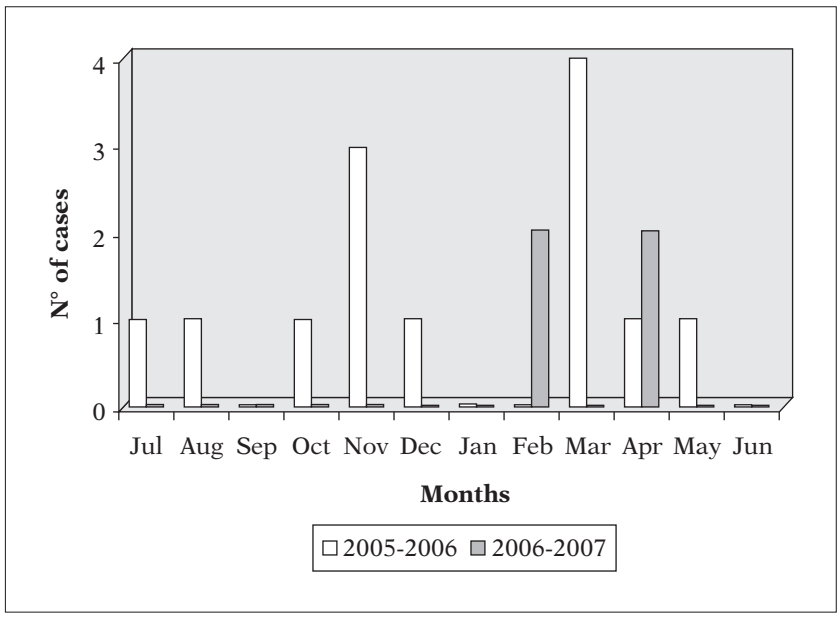

FIGURE 3 - *Monthly distribution of enteric adenovirus infections in children with acute gastroenteritis, July 2005 to June 2007.*

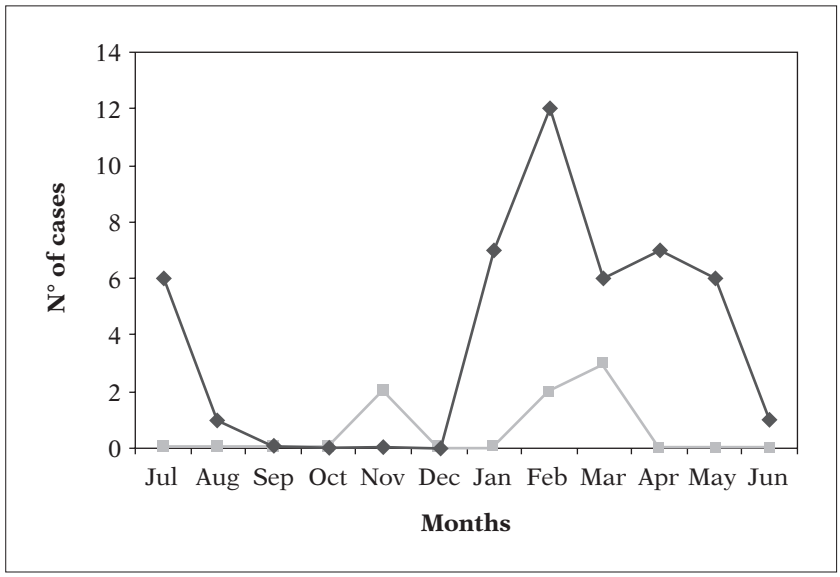

FIGURE 4 - *Monthly distribution of nosocomial rotavirus infection (♦) and nosocomial adenovirus infection (■) from July 2005 to June 2007, Latina, Italy.*

taviruses and adenoviruses. In 2006-2007, HRV was found to be associated with adenoviruses in two cases, and with *Salmonella* spp. in another two cases.

Nosocomial infections

In our study, rotaviral diarrhea acquired during hospitalization (NRV) was recorded in 46 cases (37.4%, ranging from 33.8% in 2005-2006 to 41.4% in 2006-2007).

Nosocomial rotavirus infections were mainly associated with children 13-24 months of age (13 cases), followed by infants aged from 7 to 12 months (9 cases), but they were detected in all age groups.

Nosocomial Adenovirus infections (NAV) were detected in 7 cases (41.2%, ranging from 38.5% in 2005-2006 to 50.0% in 2006-2007). 71.4% of cases occurred in children under 24 months of age. No nosocomial case of adenovirus infection was recorded among children 37-48 and 49-60 months of age.

The monthly distribution of NRV and NAV cases is shown in Figure 4. The incidence of NRV was higher in winter and spring than in the rest of the year. It is important to note that in January and February 2007, there were more NRV cases than community-acquired cases (5 vs 1, and 7 vs 5, respectively). NAV occurred in February, March, and November. Both sexes were equally affected by nosocomial infections.

DISCUSSION

Although many studies (Glass *et al.*, 1991; Grimwood *et al.*, 1995; Barnes *et al.*, 1998; Giordano *et al.*, 2001; Nguyen *et al.*, 2004) have shown the importance of acute gastroenteritis as a principal cause of morbidity and mortality in developed and developing countries, respectively, there are relatively few reports documenting the epidemiology of rotavirus and adenovirus infections in hospitalized children in Italy. Our two-year survey showed a rotavirus prevalence of 27.6% and adenovirus prevalence of 3.8% in 445 children hospitalized with acute diarrhea. These data agree with Italian and the worldwide prevalence range for hospitalized children reported by other authors (Vizzi *et al.*, 1996; Ruggeri and Declich, 1999; Medici *et al.*, 2003; Wilhelmi *et al.*, 2003; Colomba *et al.*, 2006; Van Damme *et al.*, 2007)

Most (74%) of the rotavirus infections occurred in children <3 years of age. The highest prevalence was seen in children from 13 to 24 months of age (41.2%), according to other authors (Kapikian *et al.*, 2001; Nguyen *et al.*, 2004; Cicek *et al.*, 2007). Adenoviral infections showed a higher rate of detection in the 25-36 month age group (6.8%), followed by the 13-24 (6.2%) group. This is partially in agreement with previous studies reporting that most enteric adenovirus infections occurred in children younger than two years, with the high-

est incidence in infants aged from 7 to 12 months (Herrmann *et al.*, 1988; Noel *et al.*, 1994; Grimwood *et al.*, 1995; Barnes *et al.*, 1998; Lin *et al.*, 2000).

A number of studies have shown that rotavirus infection is more frequent among male than female infants (Staat *et al.*, 2002; Cardoso *et al.*, 2003; Nguyen *et al.*, 2004). In our study, rotavirus and adenovirus infections were found in higher proportion in male children than females, but this difference was statistically insignificant. No plausible explanations have yet been given for this phenomenon.

Previous studies (Cook *et al.*, 1990; Turcios *et al.*, 2006) have indicated that in developed countries with a temperate climate, rotavirus infection shows a seasonal pattern with a peak incidence in winter, whereas in developing countries with tropical or subtropical climates, seasonality is less marked and the virus circulates all year round. In our study, in the two different periods investigated, rotavirus infection cases had a different evolution. In fact, in 2005-2006, rotavirus infections were found to be more prevalent during the period January-May with a characteristic seasonal pattern and a peak in February. In 2006-2007, seasonality was less marked. This could be related to an unusual increase in cases during the summer months, many of which were of nosocomial origin. In fact, in 2006-2007, there was a reduction in the number of total cases compared to 2005-2006 (58 vs 65), and an increase in the number of nosocomial infections (24 vs 22). In our study, enteric adenovirus infections occurred predominantly during the spring (8 cases, 47.1%), in contrast with other authors who reported no major seasonal variation (Barnes *et al.*, 1998; Lin *et al.*, 2000).

Nosocomial infections were common in our survey, according to that reported in literature (Cone *et al.*, 1988, Ford-Jones *et al.*, 1990).

37.4% of cases of gastroenteritis caused by rotaviruses were of nosocomial origin. Adenovirus hospital infections accounted for 41.2% of cases and occurred predominantly in children <24 months of age. Both NRV and community-acquired rotavirus infections had the same temporal evolution. In fact, most of NRV infections occurred during the winter and the spring, with a peak in February (Figure 4). During 2006-2007, there was an increase in NRV infections compared to the preceding period (41.4% vs 33.8%). This can be explained by epidemic peaks of nosocomial infections present in July 2006 (4 cases), January 2007 (5 cases), February 2007 (7 cases).

Data regarding simultaneous infections in gastroenteritis are limited and contrasting (Oh *et al.*, 2003; Wilhelmi *et al.*, 2003; Colomba *et al.*, 2006). In our study, mixed infections were observed in 10 cases and virus-virus coinfections were more frequent than virus-bacteria coinfections. In fact, HRV was found to be associated with adenovirus in 6 cases (1.3%), and with *Salmonella* spp. in 4 cases (0.9%).

In summary, the aim of the present study was to extend the knowledge of rotavirus and enteric adenovirus infections in hospitalized children in Italy.

In particular, this paper has confirmed that human rotaviruses are among the most important etiological agents of diarrhea in hospitalized children in Italy, while enteric adenoviruses play a limited role. Nosocomial acquisition was very common for both infections in this study.

In conclusion, regional epidemiological information on rotavirus and adenovirus infections may be important to devise strategies for intervention and for an improved use of the rotavirus vaccine. Our research confirms that continuous surveillance and monitoring of acute gastroenteritis caused by rotavirus and enteric adenovirus is needed to monitor the potential adverse effects of these pathologies. Moreover, improvements in hygiene and sanitation could significantly reduce hospital infections.

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